

REMARKS

Reconsideration of the present application is respectfully requested in view of the following remarks. Claims 43-50 are pending and under examination.

REJECTIONS UNDER 35 U.S.C. § 103

A. Claims 43-45 and 48 stand rejected under 35 U.S.C. § 103(a) for alleged obviousness over Zimmer et al. (U.S. Patent No. 6,022,875). The Examiner asserts that Zimmer et al. teach a method for treating neuropathic pain by administering opioids such as morphine together with non-opioid pyridylcarbamates such as flupirtine.

B. Claim 46 stands rejected under 35 U.S.C. § 103(a) for alleged obviousness over Zimmer et al. in view of Perovic et al. (*Neurodegeneration*. 4:369-374, 1995). The Examiner relies on Zimmer et al. as above, and alleges that Perovic et al. teach that flupirtine causes very little drowsiness. The Examiner then asserts that because the claims encompass negligible amounts of opioid, it would have been obvious to prepare a composition in which an opioid does not induce overt sedation in the presence of flupirtine.

C. Claim 47 stands rejected under 35 U.S.C. § 103(a) for alleged obviousness over Zimmer et al. in view of Devulder et al. The Examiner relies on Zimmer et al. as above, and asserts that claimed dosage range of flupirtine falls within the range taught by Devulder et al. The Examiner then asserts that it would have been obvious to combine the two references in the manner claimed.

D. Claims 49-50 stand rejected under 35 U.S.C. § 103(a) for alleged obviousness over Zimmer et al. in view of Cleary (*Cancer Control*. 7:120-31. 2000). The Examiner relies on Zimmer et al. as above, and alleges that Cleary teach that cancer pain has a neuropathic component.

Applicants respectfully traverse these rejections and submit that the instant claims satisfy the requirements of non-obviousness, because the Examiner has not established a *prima facie* case of obviousness. See *In re Mayne*, 104 F.3d 1339 (Fed. Cir. 1997) (The USPTO has the burden of showing a *prima facie* case of obviousness). In this regard, the cited references not

only fail to fairly teach or suggest all of the claim features, but fail to provide any apparent reason or motivation to practice the presently claimed methods. *See KSR v. Teleflex, Inc.*, No 04-1350 at 4, 14 (U.S. Apr. 30, 2007) (“A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art”). The instant claims are also supported by strong secondary considerations of non-obviousness, including their *synergistic effects* in treating neuropathic pain.

The generic disclosure of Zimmer et al. fails to fairly teach or suggest the specific selection of flupirtine together with an opioid for treating neuropathic pain. Even assuming that a claimed species or subgenus is encompassed by a genus of the cited art, this reason is not sufficient by itself to establish a *prima facie* case of obviousness. M.P.E.P. § 2144.08, citing *In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994). The Examiner must establish that it would have been obvious to make the claimed invention as a whole, *i.e.*, to select the claimed species or subgenus from the disclosed cited art genus. M.P.E.P. § 2144.08(II)(a)(4).

Here, Zimmer et al. provide insufficient reason or motivation to make the claimed composition. Instead, they focus on the use of substituted 2,4-imidazolidinediones, which may be optionally combined with an opioid and/or a non-opioid. Zimmer et al. provide a laundry list of non-opioids from which to choose, one of which is flupirtine. To arrive at a composition that comprises flupirtine and an opioid, it would have been necessary to first combine the substituted 2,4-imidazolidinedione of Zimmer et al. with an opioid, further combine a non-opioid into that mix, and then specifically select flupirtine from the laundry list of non-opioids. The presently claimed composition is therefore many steps removed from the generic disclosure of Zimmer et al., and this reference provides no motivation or reason to perform these specific steps. Accordingly, Applicants respectfully submit that it would *not* have been obvious to select the claimed species or subgenus from the disclosed genus of Zimmer et al., and therefore submit that claim 43-45 and 48 are non-obvious over that reference.

As to claims 46-47 and 49-50, Applicants further submit that these claims are non-obvious over the cited references. Mainly, Perovic et al., Devulder et al., and Cleary alone or in combination fail to remedy the deficiencies of Zimmer et al., because none of these references is concerned with the use of flupirtine together with an opioid for treating neuropathic

pain. Since claim 43 is non-obviousness over the primary reference Zimmer et al., dependent claims 46-47 and 49-50 are likewise non-obvious over the combination of references that rely on Zimmer et al., as in sections B-D above.

As previously made of record, Applicants also submit that the non-obviousness of the instant claims is supported by secondary considerations, such as improved properties and unexpected results. *See, e.g., In re Dillon*, 919 F.2d 688, 692, 693 (Fed. Cir. 1990). In this regard, it is respectfully submitted that *synergism* may point toward non-obviousness. *See* M.P.E.P. § 2141(I). Here, the combination of flupirtine and an opioid *synergistically* reduces pain symptoms (*see, e.g.,* page 45, lines 4-16 of the specification), thereby allowing the use of reduced levels of opioids during neuropathic pain therapy. As further evidence of the synergism achieved by the claimed combination of flupirtine and an opioid, Applicants will provide the Examiner with a § 1.132 Declaration having a detailed analysis of relevant experiments. To summarize briefly for now, these experiments show that the same amount of analgesia can be achieved with a combination of flupirtine and morphine (*e.g.,* 4:1) as is obtained using the drugs individually, but with only **10% of the ED₅₀ doses** of each drug in the fixed combination – allowing **a 90% reduction** in the dose of each individual drug. These synergistic results, in which the claimed combination provides a result that is greater than would have been expected for the sum of the individual components (*i.e.,* a greater than additive result), demonstrate that flupirtine in combination with an opioid allows a therapeutically significant reduction in the amount of either drug administered in order to obtain an analgesic effect, specifically for neuropathic pain.

Moreover, the cited references fail to provide any reason to expect the improved and synergistic properties shown by Applicants for the claimed combination of flupirtine and an opioid for treating neuropathic pain. *See In re Corkill*, 711 F.2d 1496 (Fed. Cir. 1985), citing *Ex parte The Nutrasweet Company Co.*, 19 U.S.P.Q.2d 1586 (BPAI 1991). For instance, as discussed above, Zimmer et al. focus on entirely different subject matter, mainly the use of substituted 2,4-imidazolidinediones. Also, because they provide insufficient reason to select the specific combination of flupirtine and an opioid, then they can hardly provide a reason to expect such a combination to achieve synergistic results in treating neuropathic pain. As previously

made of record, this unexpected benefit is therapeutically significant in the treatment of neuropathic pain, because the use of opioids is often frequent and sustained due to the diminished effects of opioids in subjects suffering from neuropathic pain. Such over use is often associated with addiction, the development of tolerance, and an increase in the number and severity of side effects associated with opioid use (*see, e.g.*, page 4, lines 8-11 of the instant specification). Among other benefits, these ***synergistic effects*** allow those undergoing neuropathic pain management therapy to reduce the risk of tolerance, avoid the life-interfering effects of overt sedation (*see, e.g.*, page 14, lines 23-29 of the instant specification), as well as manage other side effects, including euphoric effects, emetic effects, spastic constipation and increased smooth muscle tone (*see, e.g.*, page 4, lines 11-12 of the instant specification). Therefore, the ***unexpected and synergistic results*** demonstrated by Applicants provide real-world benefits in neuropathic pain therapy, and are clearly greater than those that would have been expected from the cited art to an unobvious extent.

In view of deficiencies in the cited references, and also in view of the secondary considerations of non-obviousness (*i.e.*, unexpected synergism), Applicants submit that the instant claims satisfy the requirements of non-obviousness under 35 U.S.C. § 103(a), and respectfully request withdrawal of this rejection.

Applicants believe that all of the claims in the application are allowable.
Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this
Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,
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